DETAILED ACTION

Claims 17-37 are pending. Claims 1-16 were cancelled in a preliminary amendment. Claims 24-25 and 27-28 are withdrawn as being drawn to a non-elected species. Claims 17-23, 26, and 29-37 are under consideration in the instant office action.

Election/Restrictions

Applicant's election without traverse of 1) desmopressin as the pharmaceutical agent, (2) emulsion as the form of the preparation, and (3) spray as the delivery form in the reply filed on 3/31/08 is acknowledged. Upon reconsideration the species election for the preparation form and delivery form are withdrawn.

Claims 24-25 and 27-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/31/08.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claim 36 is objected to because of the following informalities: there is an extra dot after the claim number in claim 36. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-23, 26, 29-30, and 32-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17 and 37 are vague and indefinite, because said claims recite that the pharmaceutical preparation (claims 17 and 37) claimed or prepared (claim 37) is characterized by having a substantially improved ciliary tolerability. Applicants' specification does not define what is meant by the term substantially, thus, an ordinary skilled artisan would be unable to ascertain the metes and bounds of substantially improved ciliary tolerability. Furthermore, the phrase "improved ciliary tolerability" is unclear, because the claims do not provide a standard of ciliary tolerability, which could be utilized to ascertain what constituted an improved ciliary tolerability.

Claim 17 recites the limitation "the pH" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 37 is also vague and indefinite, because it is unclear what is meant by the phrase "primarily comprising a malic acid compound;" and because the term "primarily comprising" is not defined in Applicants' specification. Thus, an ordinary skilled artisan would be unable to ascertain the metes and bounds of the claim limitation reading, "primarily comprising a malic acid compound."

The remaining claims are rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17-23, 26, 29, 31-34, and 37 are rejected under 35 U.S.C. 102(b) or 102(e) as being anticipated by Scheidl et al. (WO 01/60394 [IDS reference], "Scheidl-WO") or Scheidl et al. (US 2003/0119728, "Scheidl"), respectively, wherein US 2003/0199728 is being used as the English language equivalent of WO 01/60394. All citations set forth herein below are for both rejections and are from US 2003/0199728.

The applied reference has common inventors (i.e. Scheidl, Hantlich, and Hesse) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicants claim (1) a buffered pharmaceutical preparation comprising (a) at least one nasally administrable active pharmaceutical ingredient (e.g. desmopressin), (b) at least one preservative comprising benzalkonium chloride, (c) at least one buffer keeping the pH at 4 to 6, said at least one buffer comprising a malic acid compound, and (d) at least one agent selected from the group consisting of an osmotic agent and a wetting agent, said preparation having substantially improved ciliary tolerability; (2) a method of treating a condition selected from the

group consisting of allergy, bleeding disorder, diuretic impairment, and osteoporosis, comprising intranasal administration of the preparation of (1); and (3) a method of preparing the preparation of (1) comprising (i) providing water, (ii) admixing at least one nasally administrable active pharmaceutical ingredient (e.g. desmopressin), (iii) admixing at least one preservative comprising benzalkonium chloride and at least one agent selected from the group consisting of an osmotic agent and a wetting agent, and (iv) buffering the preparation to a pH of 4-6 with at least one buffer primarily comprising a malic acid compound.

Scheidl discloses **stable aqueous buffered pharmaceutical preparations suitable for nasal**, oral, or sublingual **administration** (title, abstract, [0001]) comprising (a) 0.10 mg/ml desmopressin acetate (i.e. an active pharmaceutical ingredient), (b) 0-0.20 mg/ml benzalkonium chloride (i.e. a preservative), (c) buffer **comprising DL-malic acid, D-malic acid, L-malic acid, or a mixture of malic acid and sodium acetate in a concentration of 2.5 mM (i.e. 2.5 millimoles per liter)** in [0013] (see entries 1-2 and 11-14 in the table in [0013]) as well as an aqueous composition in claim 13 of Scheidl comprising (a) **0.10 mg/ml desmopressin acetate (i.e. an active pharmaceutical ingredient), (b) 0-0.20 mg/ml benzalkonium chloride (i.e. a preservative), (c) DL-malic acid in a concentration of 2.5 mM (i.e. a buffer), (d) NaCl (i.e. osmotic agent), wherein said composition has a pH of about 5**. Claim 16 of Scheidl, discloses that the preparation of claim 13 is nasally administrable. Scheidl's claims 19-20 implicitly disclose **methods of treating antidiuretic disturbances** (e.g. *enuresis nocturna* or diabetes *insipidus*) or **haemorrhagic diseases** (e.g. hemophilia A) by **[nasal] administration of the composition disclosed in Scheidl's claim 16**. Scheidl's nasally administrable buffered desmopressin formulations **may contain additional buffers** (Scheidl claim 9), such as

acetate/acetic acid, as well as **malic acid in the form of a salt, such as the sodium salt** (i.e. sodium malate) (Scheidl claim 14). In [0007] Scheidl discloses that **suitable low concentrations of malic acid are preferably within the range of 1-5 mM**.

Scheidl discloses a method of preparing the nasally administrable buffered desmopressin solution formulations with a total volume of 1 L comprising **(a) providing water ([0014]-[0016]), (b) admixing sodium chloride (i.e. NaCl, an osmotic agent) and buffer (e.g. 0.335 g malic acid, which yields a final concentration of 2.5 mM of malic acid buffer) ([0017]), (c) admixing desmopressin acetate [0018], if necessary, (d) admixing preservative (usually benzalkonium chloride), (e) adjusting the pH with 1 N NaOH solution to at most 5.0 ± 0.2 [0020]**, and (f) sterile filtration of the final solution with a milipak sterile filter [0022]. Admixture of buffer, reads on the step of buffering the preparation. The buffered solution prepared by Scheidl's method would necessarily have a pH within the range recited in Applicants' claim 37; because the amount of buffer added in Scheidl's method falls squarely within the amount indicated in Applicants' claim 18 as being suitable for keeping the pH in the range of 4 to 6. It is noted that the addition of buffer disclosed by Scheidl (i.e. malic acid) to water reads on the step of buffering the preparation with at least one buffer at least primarily comprising a malic acid compound.

Regarding the recited property of substantially improved ciliary tolerability, Scheidl is silent; however, because Scheidl discloses the same pharmaceutical preparation claimed by Applicants, Scheidl's preparations must also inherently exhibit the same improved ciliary tolerability. Regarding the properties recited in instant claims 32 and 33; these properties are

inherently present in the preparations disclosed by Scheidl, because Scheidl's preparations are the same as Applicants' preparation claimed in claim 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheidl et al. (WO 01/60394 [IDS reference], "Scheidl-WO") or Scheidl et al. (US 2003/0119728, "Scheidl"), respectively, wherein US 2003/0199728 is being used as the English language equivalent of WO 01/60394.

Applicant Claims

Applicants' claims have been generally described above, and claims 35 and 36 require that the method administers the preparation of claim 17 via a nasal spray (claim 35) or via nose drops (claim 36).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Scheidl and Scheidl-WO have been set forth above in the instant office action.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Scheidl does not anticipate the rejected claims, because Scheidl does not exemplify a method of administering Applicants' formulation in the form of a nasal spray or nasal drops. This deficiency is obvious per the teachings of Scheidl.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of the instant application to administer Scheidl's invented preparation in the form of a nasal spray, because Scheidl exemplifies a nasal spray formulation in Example 2. Thus, an ordinary skilled artisan would have been reasonably motivated to administer Scheidl's invented preparations in the form of a nasal spray. It is noted that a broad reasonable interpretation of an aqueous nasal spray reads on nose drops, because the act of spray an aqueous formulation necessarily will produce droplets of said formulation. The application of a sprayed liquid formulation to the nose reads on nasal drops, because the sprayed aqueous liquid formulation necessarily contacts the nasal surface in the form of droplets. It is noted that Applicants' specification does not define nasal drops to have any particular size. Therefore, for the aforementioned reasons an ordinary skilled artisan would have had a reasonable expectation of successfully administering Scheidl's preparations as either a nasal spray or nasal drops. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 17-23, 26, 29-30, and 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. (U.S. Patent No. 5,514,670) in view of Scheidl et al. (WO 01/60394 [IDS reference], "Scheidl-WO"), wherein US 2003/0199728 is being used as the English language equivalent of WO 01/60394.

Applicant Claims

Applicants' claims have been generally described above, and claim 30 requires that the composition be in the form of an emulsion.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Friedman teaches submicron **lipid-in-water bioadhesive emulsions** for the delivery of **biologically active peptides** to mucous surfaces, including **nasal mucosa** (Title; abstract; col. 1, lines 5-10). The advantages of Friedman's invented submicron emulsions is that said formulations (a) prolong the residence time in situ, thereby decreasing the required dosing frequency of peptide drug and (b) allows for the localization in the specified region to improve and enhance targeting and bioavailability of delivered proteins (i.e. improved bioavailability) (col. 3, lines 24-39). **The continuous phase of the emulsion is aqueous** and may contain **salts**, sugars, antioxidants, **preservatives**, microbiocides, **buffers, osmoticants**, etc. (col. 4, lines 41-44). The biologically active peptide may be hydrophilic, hydrophobic, or amphiphilic (col. 4, lines 45-49). Suitable bioactive peptides, including proteins, which are suitable, include, for example, calcitonin (col. 6, line 65; Example 2: col. 12, line 46 through col. 13, line 62; claim 23), desmopressin and analogs (col. 7, line 19 and claim 24). Friedman teaches a method of administering a bioactive peptide by application to a mucosal surface (e.g. nasal) a lipid-in-water emulsion comprising a plurality of particles each having a hydrophobic core, a bioactive peptide, a surfactant, and an aqueous continuous phase (claim 36). Friedman teaches the step of making the aqueous solution utilized to make the lipid-in-water emulsions, comprising the steps of admixing buffer, water, bioactive peptide, bioadhesive polymers, preservatives, and other additives (col. 9, lines 4-30). The method of preparing the emulsions is described in Freidman in section 5.8 (col. 10, line 21 through col. 11, line 5).

The teachings of Scheidl/Scheidl-WO have been set forth above in the instant office action.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Friedman lacks the teaching of compositions comprising malic acid buffer, benzalkonium chloride as a preservative, and specific osmotic agents (i.e. osmoticants). This deficiency is cured by the teachings of Scheidl.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to combine the teachings of Friedman and Scheidl to obtain stable buffered aqueous emulsions of biologically active peptides, because both Friedman and Scheidl teach aqueous formulations comprising biologically active peptides (e.g. desmopressin) intended for nasal administration. An ordinary skilled artisan would have been motivated to include a known buffer, such as malic acid, in Friedman's compositions, because Friedman explicitly suggests the inclusion of buffers and Scheidl demonstrates that malic acid buffer in amounts of 1-5 mM provide stable aqueous desmopressin formulations. An ordinary skilled artisan would have been motivated to include benzalkonium chloride and sodium chloride in Friedman's formulations per the teachings of Scheidl; because Friedman explicitly suggests that the invented aqueous emulsions may comprise preservatives and osmoticants, benzalkonium chloride is a known preservative (Scheidl), and sodium chloride is a known osmotic agent. For these reasons an ordinary skilled artisan would have had a reasonable expectation of successfully modifying Friedman's compositions to comprise benzalkonium chloride, malic acid and other buffers, and sodium chloride. Regarding the method of treatment, both Friedman and Scheidl teach formulations comprising desmopressin. Scheidl's teaching of a method of treating a

disease known to be treatable by administration of desmopressin would render it obvious to administer Friedman's invented emulsions nasally to treat diuretic impairment, for example. Furthermore, the use of a known biologically active peptide in the manner for which it is known as being suitable in the prior art is necessarily prima facie obvious. Regarding administration of the composition in the form of a nasal spray or nasal drops, it would have been prima facie obvious at the time of the instant application to administer Scheidl's invented preparation in the form of a nasal spray, because Scheidl exemplifies a nasal spray formulation in Example 2. Thus, an ordinary skilled artisan would have been reasonably motivated to administer Friedman's formulations as modified by Scheidl's teachings in the form of a nasal spray. It is noted that a broad reasonable interpretation of an aqueous nasal spray reads on nose drops, because the act of spray an aqueous formulation necessarily will produce droplets of said formulation. The application of a sprayed liquid formulation to the nose reads on nasal drops, because the sprayed aqueous liquid formulation necessarily contacts the nasal surface in the form of droplets. It is noted that Applicants' specification does not define nasal drops to have any particular size. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Conclusion

Claims 17-23, 26, and 29-37 are rejected. Claim 36 is objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/James H Alstrum-Acevedo/
Patent Examiner, Art Unit 1616
Technology Center 1600